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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,926	07/31/2003	Carlo Riccardi	RICCARDI=1A	7576

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,926	RICCARDI, CARLO	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,17-19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,17-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/17/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/403,861.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 19, 2006 has been entered.

DETAILED ACTION

Please note the examiner of record has changed, the examiner is now Joseph Woitach, and the group art unit is 1632.

This application filed July 31, 2003, is a CIP of 09/403,861, filed February 11, 2000, now US PAT 6,833,348, which is a national stage filing of PCT/EP98/02490, filed April 27, 1998.

Applicant's amendment filed July 19, 2006, has been received and entered. Claims 1, 2, 5-16 and 20 have been cancelled. Claim 21 has been added. Claims 3 and 19 have been amended. Claims 3, 4, 17-19, 21 are pending.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on April 25, 2005 was acknowledged. No new arguments are provided. The requirement is still deemed proper and maintained as FINAL.

Newly added claim 21 is drawn to the elected invention.

Claims 3, 4, 17-19, 21 are pending and currently under examination.

Priority

As indicated throughout prosecution, the effective filing date of the claimed invention is the filing date of the instant application, which is July 31, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4, 17-19, 21, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In this case, at issue is that claims 3 and 19 have been amended to recite a specific phenotype of the resulting transgenic mouse that is not consistent with the breadth of the remaining portion of the claim. More specifically, the phenotype is consistent only in aged mice. More importantly, it appears to only be supported by the working examples provided in the instant specification so would be restricted to the specific DNA construct, i.e. specific promoter and GILZ trangene expressed. The specification and art of record details the unique control that the h CD2 locus

control region provides for expression, and the potential role of GILZ(s) in a variety of other tissues. The present specification provides for a single combination of promoter and transgene that results in a unique phenotype when used to generate a transgenic mouse as now claimed. Applicant points to page 84 for support of the present claim amendments. See remarks section pages 5-6. Applicant's support is noted, however these pages further support the position that the phenotype is consistent with one specific transgenic mouse, not the breadth as instantly claimed.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 3, 4, 17-19, 21, are also rejected under 35 U.S.C. 112, first paragraph,

as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described. More specifically, claims 3, 4, 17-19 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse with a nucleic acid construct comprising an 874 bp mouse GILZ cDNA operably linked to a human CD2 promoter and a human CD2 locus control region integrated into its genome, wherein said mouse expresses the GILZ protein in its T-cell lineage at an elevated level, compared to a non-transgenic mouse, wherein the elevated level of GILZ protein expression results in a significant decrease in CD4.sup.+CD8.sup.+ double positive, and increases in CD4.sup.-CD8.sup.- double negative, CD8.sup.+ single positive cells, and the CD4.sup.+ subpopulation, compared with a non-transgenic mouse and methods of use, does not reasonably provide enablement for a transgenic mouse with any nucleic acid construct comprising any GILZ sequence from any species operatively linked to any mammalian T-cell lineage specific promoter sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant notes that the specification "discloses mammalian GILR (GILZ) cDNA sequences" (page 7 of 8), and argues that coupled with the general knowledge in the art at the time of the claimed invention one of ordinary skill in the art could have practiced the invention as claimed, citing MPEP 2164.01 in support of their position (pages 7-8). Applicant's arguments have been fully considered, but not found persuasive as they apply to the instant rejection.

As noted previously, transgene promoters and expression of a transgene do not function in isolation from the remaining genome. Instead, a transgene's expression level and pattern of tissue expression is affected by its integration site, which can lead to repressed expression or leaky expression depending on the promoter used. The term T-cell lineage specific promoter encompasses the entire lck promoter system. This system contains a distal and proximal promoter, of which the proximal promoter contains a transcriptional repressor (Muise-Helmericks *et al.* (1995) J. Biol. Chem. 270:27538-27543; Abstract; pg. 27538, first column). This system regulates both the developmental and cell type expression of lck (pg. 27538, first column). Such a promoter system would not reasonably be predicated to produce the same disclosed phenotype as the instant mouse. Further, the specification discloses that the promoter and LCR of hCD2 were used to make the claimed mouse because they confer 3 important features to the hCD2-mGILR transgene: tissue specificity; cop-dependence; and position-independent expression (Specification pg. 89, Results). This a specific and clever system designed to overcome the problems with integration discussed above. The skilled practitioner would not predict that any other T-cell lineage specific promoter system, by itself, would reliably produce the claimed phenotype, since such a promoter would lack the hCD2 LCR. Further, the specification discloses that a GO-TG mouse is used as a model to study the effects on T cell development due to constitutive GILR over-expression (Specification, pg. 90, section C). The phenotype of transgenic animals is affected by multiple factors other than the sequence of a transgenic construct; such as the specific site of transgene integration into the genome (positional effect), the level of expression, chromatin organization, and the pleiotropic effects of the transgene and interactions with other gene products. Therefore the phenotype of any given

transgenic mouse cannot be predicted based solely on the sequence of a transgenic construct.

More generally, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the vector used, and the specific site of transgene integration into the genome (positional effect), for example, are all important factors in controlling the expression of a transgene in the production of transgenic mammals which exhibits a resulting phenotype. In this case, the claims as amended now require a specific phenotype, however the art would support that this would only be accomplished in vivo with the specific combination reduced to practice in the working examples of this disclosure, not as broadly claimed. Again, this general observation is supported by Houdebine *et al.*, who states that "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" {Houdebine *et al.* (2000) Transgenic Research 9:305-320; pg. 309, second column:The expression of transgenes}. Further, Houdebine *et al.* states that the potency of any transgene can only be estimated in transgenic mammals and the level of expression of transgenes in mice is not predictive of their levels in other mammals (pg. 310, first column). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, first column). See also Kolb *et al.*, who states that "the expression of foreign genes in transgenic mammals is generally unpredictable as transgenes integrated at random after pro-nuclear injection into fertilized oocytes" because of inhibition by neighboring chromatin (Kolb *et al.* (1999) Gene

227:21-31; Abstract). The mere contemplation and recitation of possible promoters is not enough to provide enablement for any transgenic mouse containing a transgene comprising said promoter(s) for the reasons stated above and the problems cited in the art.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Delfino *et al.* Blood. 2004 Dec 15;104(13):4134-41. Epub 2004 Aug 19, Decrease of Bcl-xL and augmentation of thymocyte apoptosis in GILZ overexpressing transgenic mice, is post filing art that provides further support for the importance of the hCD2 vector for expression (page 4139, second column). While a role for GILZ had been proposed in the thymus, its specific pathological affect *in vivo*, in particular in T-lymphocytes provided a model for studying various sub-populations of lymphocytes, and possible roles in pathological alterations (page 4140).

Conclusion

No claim is allowed.

The claims are free of the art of record because while it was generally known that over-expression of GLZ would affect apoptosis in T-cells (see for example D'Adamino, Dec.1997-

IDS ref), one could not have predicted that expression in T-cells would have led to the specific affects on the various subpopulations *in vivo* as required by the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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